CAT PELT, STANDARDIZED - felis catus skin injection, solution
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ALK-Abello, Inc.

ALLERGENIC EXTRACT
STANDARDIZED CAT PELT
(Felis domesticus)

WARNINGS

Standardized allergenic extract is intended for use by physicians who are experienced in the administration of allergenic extracts for immunotherapy and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist. Standardized Cat Pelt extract is not interchangeable with standardized Cat Hair extract or with any non-standardized Cat extracts. Standardized allergenic extracts are not directly interchangeable with allergenic extracts of the same-labeled potency from different manufacturers. The patient must be re-evaluated with the newly selected extract. The initial dose must be based on skin testing as described in the dosage and administration section of this insert. Patients being switched from other types of extracts standardized or unstandardized cat extracts from other suppliers, to this standardized allergenic extract should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. As with all allergenic extracts, severe systemic reactions may occur. Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk. In certain individuals, these life-threatening reactions may rarely result in death. Patients should be observed for 20 to 30 minutes following treatment, and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction.
This product should not be injected intravenously. Deep subcutaneous routes have proven to be safe. See the warnings, precautions, adverse reactions and overdosage sections below.
Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death.
Adverse events are to be reported to MedWatch (1-800-FDA-1088), Adverse Experience Reporting, HFM-210 Center for Biologics Evaluation & Research, Food & Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.
Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to the warnings, precautions and adverse reaction sections below.

DESCRIPTION

Standardized Allergenic Extract in the accompanying vial is a sterile solution and contains glycerin 50% v/v and phenol 0.4% (preservative). Inert ingredients include sodium chloride. It is intended for percutaneous testing, intradermal testing and subcutaneous injection.
Glycerinated cat pelt extracts are prepared from defatted & dried cat pelts extracted in phenol saline, concentrated, dialyzed, glycerinated, filtered aseptically, and dispensed in multidose vials. These are subsequently tested for sterility, safety and potency. This is a Standardized Cat Pelt Extract and is not interchangeable with Standardized Cat Hair Extract from this or other manufacturers (See Warnings) Standardized Cat Pelt extract contains Cat allergens in addition to *Fel d I* (Cat I). Biologic potency with this product has been assessed by quantitative intradermal skin testing.[1] For ease in use and for lot to lot consistency, the potency of each standardized Cat Pelt lot is expressed relative to an FDA reference in Bioequivalent Allergy Units (BAU's) per milliliter. BAU's are assigned to standardized cat preparations based on major allergen content, *Fel d I* (Cat I), using official FDA methods and reagents.[2] BAU's have been shown by FDA to correlate with clinical allergenicity. (See table below)
Table: Major Allergen Content /BAU

Fel d I (u/mL)	BAU/mL
10-19.9	10,000
5-9.9	5,000

CLINICAL PHARMACOLOGY

Diagnostically (for skin testing) the allergen combines with IgE antibodies fixed to mast cells in the skin.[3] This complexing causes an increase in cellular permeability and degranulation of the mast cells releasing chemical mediators. These mediators (such as histamine) are responsible for a local inflammatory response of wheal and erythema typical of a positive skin test reaction and also, the symptoms commonly associated with allergic disease. The more mediator release, the larger the reaction (wheal and erythema).

Treatment consists of the subcutaneous injection of gradually increasing doses of the allergens to which the patient is allergic. It has been demonstrated that this method of treatment induces an increased tolerance to the allergens responsible for the symptoms on subsequent exposure. Although the exact relationships between allergen, skin sensitizing antibody (IgE) and the blocking antibody (IgG) have not been precisely established, clinically confirmed immunological studies have adduced evidence of the efficacy of hyposensitization therapy.

Numerous controlled studies have demonstrated the clinical efficacy of immunotherapy with cat, dust mites and some pollen extracts.[4] Nevertheless, responses are not uniform but variable, and in a few studies, the majority of the patients reported no appreciable improvement.

INDICATIONS AND USAGE

This product is indicated for the diagnosis and treatment (hyposensitization therapy) of patients who experience allergic symptoms due to exposure to cats and who exhibit type I skin sensitivity when tested to those specific allergens.
Hyposensitization (injection) therapy is a treatment for patients exhibiting allergic reactions to seasonal pollens, dust mites, molds, animal danders, and various other inhalants, in situations where the offending allergen cannot be avoided.
Prior to the initiation of therapy, clinical sensitivity should be established by careful evaluation of the patient's history confirmed by diagnostic skin testing. Hyposensitization should not be prescribed for sensitivities to allergens which can be easily avoided.

CONTRAINDICATIONS

There are no known absolute contraindications to immunotherapy. However, a patient should not be immunized with preparations of allergens to which the patient has not demonstrated symptoms and positive skin tests. In most cases, immunotherapy is not indicated for those allergens that can be eliminated or minimized by environmental control.

Also, there is some evidence, although inconclusive, that routine immunizations may exacerbate autoimmune diseases.[5,6,7] Hyposensitization should be given cautiously to patients with this predisposition. Patients with severe cardiorespiratory symptoms are at additional risk during a systemic reaction. The physician must weigh the risk to benefit in these cases.

WARNINGS

See warnings at beginning of this package insert. Standardized allergenic extracts may be more potent than non-standardized extracts. This cat extract may be compositionally different than unstandardized and standardized extracts from other suppliers.
This cat extract is prepared from cat pelt and should not be interchanged with Standardized Cat Hair Extract or Standardized Cat Pelt Extract from other sources. This product has been assigned a bioequivalent allergy unit (BAU) designation based on both *in vivo* and *in vitro* potency measures. The physician should perform skin tests to determine the initial starting dose for standardized extracts.
From standardized aqueous extracts from other manufacturers to ALK-Abello standardized aqueous extracts: The physician should establish the potency relationship, perhaps by comparative skin testing at equal concentration, prior to injecting the first standardized dose.
Patients should always be observed for at least 20 to 30 minutes after any injection. In the event of a marked systemic reaction, application of a tourniquet above the injection site and administration of 0.2 mL to 1.0 mL (0.01 mg/kg) of Epinephrine Injection (1:1,000) is recommended. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet is then gradually released at 15 minute intervals. Patients under treatment with beta-blockers may be refractory to the usual dose of epinephrine.
Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalation bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. In cases of respiratory obstruction, oxygen and intubation may be necessary. Life-threatening reactions unresponsive to the above may require cardiopulmonary resuscitation.
PRODUCT SHOULD NOT BE GIVEN INTRAVENOUSLY.
In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself. If the protective action of allergenic extract injections is considered essential for the patient's welfare, appropriate symptomatic therapy with antihistaminic, adrenergic or other drugs might be needed either prior to or in conjunction with the allergenic extract injections.
Withhold allergenic extracts temporarily or reduce the dose in patients with any one of the following conditions:

- Severe rhinitis or asthma symptoms;
- Infection or flu accompanied by fever;
- Exposure to excessive amounts of clinically relevant allergen prior to therapy.

PRECAUTIONS

Information For Patients: Patients should be instructed to describe any active allergic symptoms such as rhinitis, wheezing, dyspnea, etc. prior to injection including any late reactions from previous administration. Patients should be instructed to remain in the office for 20 to 30 minutes after injection to monitor for adverse reactions. Also, see **ADVERSE REACTIONS** and **WARNINGS** sections.

GENERAL

1. In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself. Objective assessment of pulmonary

function such as Peak Expiratory Flow Rate (PEFR) before allergen administration and prior to discharge may be useful in unstable asthmatics to reduce the chances of exacerbation of the patient's asthma. If the protective action of allergenic extract injections is considered essential for the patient's welfare, appropriate symptomatic therapy with antihistaminic, beta-adrenergic or other drugs might be needed either prior to or in conjunction with the allergenic extract injections.

2. Store allergenic extracts between 2º and 8ºC at all times, even during use.

3. Injections are to be given subcutaneously with the usual sterile precautions using a Tuberculin syringe.

4. Care must be taken to avoid injecting into a blood vessel. Pull gently on syringe plunger to determine if a blood vessel has been entered (See boxed Warnings).

5. Allergenic extracts slowly become less potent with age. During the course of treatment, it may be necessary to continue therapy with a vial of extract bearing a later expiration date. The initial dose of the extract bearing the later expiration date should be reduced by at least 75% of the amount of the dosage from the previous extract.

6. Use standard aseptic precautions when making dilutions.

7. Extracts in 50% glycerin can cause discomfort at the site of the injection during the injection. Glycerinated extracts diluted for intradermal testing must be diluted at least twenty-five-fold to less than 2% glycerin (by volume) as glycerin above this level can cause false positive intradermal skin tests. Use of negative control skin test containing an equal concentration of glycerin as the allergen when evaluating intradermal skin tests is recommended.

PREGNANCY - CATEGORY C:
Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
Controlled studies of hyposensitization with moderate to high doses of allergenic extracts during conception and all trimesters of pregnancy have failed to demonstrate any risk to the fetus or to the mother.[8] However, on the basis of histamine's known ability to contract the uterine muscle, the release of significant amounts of histamine from allergen exposure of hyposensitization overdose should be avoided on theoretical grounds. Therefore, allergenic extracts should be used cautiously in a pregnant woman, and only if clearly needed.

PEDIATRIC USE:
Children can receive the same dose as adults, however, to minimize the discomfort associated with dose volume it may be advisable to reduce the volume of the dose by half and administer the injection at two different sites.

NURSING MOTHERS:
It is not known if allergens administered subcutaneously appear in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Studies in animals have not been performed.

DRUG INTERACTIONS:

Drugs can interfere with the performance of skin tests.[9]
Antihistamines: Response to mediator (histamine) released by allergens is suppressed by antihistamines. The length of suppression varies and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours (chlorpheniramine), and can be as long as 40 days (astemizole).
Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine which may last for a few weeks.
$Beta_2$ Agonists: Oral terbutaline and parenteral ephedrine, in general, have been shown to decrease allergen induced wheal.
Dopamine: Intravenous infusion of dopamine may inhibit skin test responses.
Beta Blocking Agents: Propranolol can significantly increase skin test reactivity.
Other Drugs: Short acting steroids, inhaled $beta_2$ agonists, theophylline and cromolyn do not seem to affect skin test response.

ADVERSE REACTIONS
Local: Reactions at the site of injection may be immediate or delayed. Immediate wheal and erythema reactions are ordinarily of little consequence, but if very large, may be the first manifestation of systemic reaction. If large local reactions occur, the patient should be observed for systemic symptoms for which treatment is outlined below. However, systemic reactions may occur in the absence of large local reactions.
Delayed reactions start several hours after injection with local edema, erythema, itching or pain. They are usually at their peak at 24 hours and usually require no treatment. Antihistamine drugs may be administered orally.

The next therapeutic dose should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

Systemic: It should be noted that anaphylaxis and deaths following the injection of mite and other extracts have also been reported by The British Committee on Safety in Medicine[10]. Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R F, et al.[11] and by Reid, M J et al.[12]. With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and OVERDOSE could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Systemic reactions are characterized by one or more of the following symptoms: Sneezing, mild to severe general urticaria, itching other than at the injection site, extensive or generalized edema, wheezing, asthma, dyspnea, cyanosis, hypotension, syncope and upper airway obstruction. Symptoms may progress to shock and death. Patients should always be observed for 20 to 30 minutes after any injection. Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalational bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. Severe airway obstruction, unresponsive to bronchodilator may require tracheal intubation and use of oxygen. In the event of a marked systemic reaction, application of a tourniquet above the injection site and the administration 0.02 mL to 1.0 mL of Epinephrine Injection (1:1,000) is recommended. Maximal recommended dose for children under 2 years of age is 0.3 mL. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet should not be left in place without loosening for 90 seconds every 15 minutes.

The next therapeutic injection of extract should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

OVERDOSE

Signs and symptoms of overdose are typically local and systemic reactions. For a description and management of overdose reactions, refer to "Adverse Reactions" section above.

Adverse Events should be reported via MedWatch (1-800-FDA-1088), Adverse Experience Reporting, HFM-210 Center for Biologics Evaluation & Research, Food & Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particular matter and discoloration prior to administration whenever solution and container permit.

When diluting bulk extracts, use of Sterile Diluent for Allergenic Extracts or Sterile Diluent for Allergenic Extracts Normal Saline with Human Serum Albumin (HSA) are recommended. Dilutions should be made with sterile disposable syringes using aseptic technique. Commonly 10 fold dilutions are used to achieve a desired concentration for intradermal testing or initiation and continuation of immunotherapy. For example, transferring 0.5 mL of a 10,000 AU/mL extract into 4.5 mL of diluent will yield 5 mL of extract @ 1,000 AU/mL. Prepare as many additional serial dilutions as necessary to reach the appropriate concentration.

Care should be exercised to avoid cross contamination with other allergens if mixing with other allergenic extracts. The use of separate syringes for each allergen and diluent is **mandated** when compounding patient mixes.

Diagnosis - In diagnosing the sensitive individual, the symptom history must be associated with exposure to the allergen. Skin testing is used in conjunction with a definitive history for diagnosing individual sensitivities.

An excellent method of recording results is to cover the skin reaction with transparent tape, outline the erythema first then the wheal with an indelible pen, then remove the tape and transfer it to the patient's permanent record. For preferred results, it is recommended that the actual measurement of the extent of both responses be recorded. This can be accomplished by measuring the longest erythema diameter, then selecting the mid-point of that line and measuring at a 90^{o} angle to that line to determine the orthogonal diameter. The sum of these two measurements is the sum of erythema (#E); the sum of wheal diameters is determined in a similar manner. Patient's response is graded on the basis of the size of erythema and/or wheal.

Percutaneous (prick/scratch/puncture) test:

Prick, scratch, or puncture skin tests should be performed initially using an extract specially made for this purpose.

In a skin test study of 12 patients who were determined to be allergic to cat, the mean puncture test (using a bifurcated needle) to a Cat Pelt extract containing 10,000 BAU/mL had a sum of erythema of 71 mm (range 52 - 90 mm) and a sum of wheal of 15 mm (range 4 - 25 mm).

What follows are general guidelines for percutaneous testing[13]. Different devices and/or techniques influence the size of the reaction; therefore it is important to refer to the device manufacturer’s or distributor’s instructions when grading reactions. As a negative control, the diluent should be tested and included in the interpretation in the skin test reactions. Use of a positive control such as histamine base at 1 mg/mL should be used to assess skin test reactivity.

0	No reaction or less than control
+	Erythema greater than control, smaller than a nickel (21 mm diameter)
++	Erythema greater than a nickel in diameter, no wheal
+++	Wheal and erythema without pseudopods
++++	Wheal and erythema with pseudopods

Intradermal test:
On the forearm or upper outer aspect of the arm, using a 26 - 27 gauge, short bevel needle, inject intradermally 0.05 mL of the intradermal test solution. Skin whealing responses should be observed 10 - 20 minutes after administering the test.
In a skin test study of the 12 cat puncture reactive patients described previously, the mean intradermal dose for #E = 50 mm was 0.03 BAU/mL (range = 1.5 to <0.002 BAU/mL).
Intradermal testing should start with a dilute solution, usually in the range of 0.1 BAU/mL or less.
Glycerinated extracts diluted for intradermal testing may be diluted at least 25 fold to less than 2% glycerin (by volume) as glycerin above this level can cause false positive intradermal skin tests.
A negative skin test is one where the sum of erythema was 0 or equal to the sum of the wheal. As a negative control, the diluent should be tested and included in the interpretation of the skin reactions. What follows are general guidelines for intradermal tests[13].

0	No reaction or less than negative control
+	3-4 mm wheal with erythema, or erythema alone larger than a nickel (21 mm diameter)
++	4-8 mm wheal and erythema without pseudopods
+++	Over 8 mm wheal and erythema without pseudopods
++++	Wheal and erythema with pseudopods

Immunotherapy - Starting dose for immunotherapy is related directly to a patient's sensitivity as determined by carefully executed skin testing. Degree of sensitivity can be established by determination of D_{50} (the intradermal dose, base three, that produces a SE = 50 mm).[1]
A general rule is to begin at 1/10 of the dose that produces sum of erythema of 50 mm (approximately a 2+ positive skin test reaction). For example, if a patient exhibits a 2+ intradermal reaction to 1 BAU/mL, the first dose should be no higher than 0.05 mL of 0.1 BAU/mL. Dosage may be increased by 0.05 mL each time until 0.5 mL is reached, at which time the next 10-fold more concentrated dilution can be used, beginning with 0.05 mL, if no untoward reaction is observed. (See beginning of **DOSAGE AND ADMINISTRATION** section for instructions in preparing dilutions of concentrates).
If a tolerated dose of allergenic extract has been established, the initial dose from the new extract should be reduced by 75% of the previously well tolerated dose (see also Precautions).
Interval between doses in the early stages of immunotherapy is no more than once to twice a week, and may gradually be increased to once every two weeks. Generally, maintenance injections may be given as infrequently as once every two weeks to once a month. The progress of patients on immunotherapy should be closely monitored. If improvement is realized a usual course of treatment may be from 3 to 5 yeas. If progress is unsatisfactory for a year or more discontinuation of immunotherapy should be considered.
Injections are given subcutaneously preferably in the arm. It is advantageous to give injections in alternate arms and routinely in the same area. In some patients, a local tolerance to the allergen may develop thus preventing a possible severe local reaction.
After inserting the needle, but before injecting the dose, pull plunger of the syringe slightly, if blood returns in the syringe, discard the syringe and contents and repeat injection at another site.
Bulk concentrated extracts must be diluted for initial therapy and intradermal skin testing. For recommended diluent, refer to **DOSAGE AND ADMINISTRATION** section.
Withhold allergenic extracts temporarily or reduce the dose in patients with any one of the following conditions:

- severe rhinitis or asthma symptoms
- infection or flu accompanied by fever
- exposure to excessive amounts of clinically relevant allergen prior to therapy

Allergenic extracts slowly become less potent with age. During the course of treatment, it may be necessary to continue therapy with a vial of extract bearing a later expiration date. The initial dose of the extract bearing the later expiration date should be lowered to a safe non-reaction-eliciting level. When switching one standardized extract with another, at least 75% reduction in dose is suggested.
Use standard aseptic precautions when making dilutions. The first dose of the new extract should be reduced at least 50% - 75% of the amount of the dosage from the previous extract.
Stability studies for diluted and undiluted forms of this product are not complete. Indications are the undiluted product will retain its potency under recommended storage conditions at least until the expiration date on the vial label is reached. It is recommended that minimal amounts of the concentrate be diluted so that the diluted product is used up within a relatively short period of time, i.e. preferably not more than four weeks.

STORAGE:
To maintain stability of allergenic extracts, proper storage conditions are essential. Bulk concentrates and diluted extracts are to be stored at 2^{o} to 8^{o} C even during use. Bulk or diluted extracts are not to be frozen. Do not use after the expiration date shown on the vial label.

HOW SUPPLIED
For percutaneous testing, 5 mL dropper vial, 10,000 BAU/mL in glycerin 50% (v/v).

For intradermal testing, 5 mL vial, 100 BAU/mL.
For immunotherapy, 10 mL and 30 mL vials of bulk concentrate, 10,000 BAU/mL in glycerin 50% (v/v).

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